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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,268	07/11/2005	William C. Olson	2048/59331-D-PCT-US/JPW/M	1581

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EXAMINER
HUMPHREY, LOUISE WANG ZHIYING

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
02/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,268	OLSON ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-24,28-31,34 and 74-79* is/are pending in the application.

4a) Of the above claim(s) *11-16,18,24,28-31 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-10,17,19-23 and 74-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed on 09 April 2007. Claims 2-4, 25-27, 32, 33, and 35-73 have been canceled. Claims 1, 5-24, 28-31, 34, and 74-79 are pending. Claims 11-16, 18, 24, 28-31, and 34 are withdrawn. Claims 1, 5-10, 17, 19-23 and 74-79 are under final rejection.

Information Disclosure Statement

The information disclosure statement (IDS) filed on 18 June 2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. An initialed and dated copy of the 1449 form is attached to the instant Office Action.

Specification

The objection to the specification is withdrawn in light of Applicant's amendment filed on 05 October 2004.

Claim Objections

The objection to claim 9 is withdrawn in response to Applicant's amendment.

Double Patenting

The provisional nonstatutory double patenting rejection of claims 1-4, 6-10, 20 and 75-77 as being unpatentable over claims 113, 115-118, 120 and 124-126 of US

Application No. 10/489,040 in view of O'Hagan et al. (2001) is withdrawn in response to Applicant's amendment.

The nonstatutory double patenting rejection of claims 3-6, 8-10, 20 and 74-77 as being unpatentable over claims 113, 115-118, 120 and 124-126 of US Application No. 10/489,040 in view of O'Hagan et al. (2001) is withdrawn in response to Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 3-10, 20-23, and 74-79 under 35 U.S.C. §103(a) as being obvious over Barnett *et al.* (US PAT 6,602,705 B1) in view of Binley *et al.* (US PAT 7,022,324) is withdrawn in response to Applicants' amendment to claim 1.

The rejection of claims 17 and 19 under 35 U.S.C. §103(a) as being obvious over Barnett *et al.* (US PAT 6,602,705 B1) in view of Binley *et al.* (US PAT 7,022,324) and Ishikawa *et al.* (1998) is **maintained and extended to claims 1, 5-10, 20-23, and 74-79** as necessitated by Applicants' amendment.

The instant claims, as amended, are directed to a composition comprising a pharmaceutically acceptable carrier, an adjuvant, a pharmaceutically acceptable

particle, and a stable HIV-1 pre-fusion envelope glycoprotein trimeric complex operably affixed thereto, each monomeric unit of the complex comprising a modified form of a gp120 of a HIV-1 isolate and a modified form of an ectodomain of gp41 of such HIV-1 isolate, wherein the modified gp120 and the modified gp41 ectodomain are bound to each other by at least one intermolecular disulfide bond between a cysteine residue introduced into the modified gp120 and a cysteine residue introduced into the modified gp41 ectodomain, which stabilizes the otherwise non-covalent gp120-gp41 ectodomain interaction, wherein the stable HIV-1 pre-fusion envelope glycoprotein trimeric complex is operably affixed to the particle via an agent which is operably affixed to the particle. SEQ ID NO:18 is the wild type gp140 with a disulfide bond from the JR-FL strain of HIV-1. SEQ ID NO:20 is the wild type gp140 with a disulfide bond from the JR-FL strain of HIV-1 with the deletion of V1V2 region. SEQ ID NO:22 is the wild type gp140 with a disulfide bond from the JR-FL strain of HIV-1 with the deletion of V3 region.

Barnett *et al.* describe antigen-presenting and immune-stimulating compositions that include various excipients, adjuvants, carriers, modulating agents, and the like. Barnett *et al.* specifically disclose suitable carriers such as proteins, polysaccharides, polylactic acids, polyglycollic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes). Examples of particulate carriers include methacrylate polymers and PLG. Adjuvants include aluminum salts (alum), saponin, Ribi adjuvant sytem, Complete Freunds Adjuvant, Incomplete Freunds Adjuvant, cytokines such as interleukins (IL-1, IL-2, etc.), and beta chemokines (MIP, 1-alpha, 1-beta Rantes, etc.). See Abstract and column 31-32. Liposomal preparations include

cationic anionic and neutral preparations. See column 47, lines 31-67. Antigens include gp120, gp41, gp160, Gag and Pol from a variety of isolates from diverse subtypes A through G and O. See column 42, lines 13-20. One embodiment of the antigen is the HIV-1_{SF2} Env polypeptide, which can exist in both monomeric and trimeric forms. See column 57, lines 12-45. Barnett *et al.* further suggest ways to manipulate Env coding sequences to maximize gene expression: sequences encoding hypervariable regions of Env, particularly V1 and/or V2 are deleted; N-glycosylation sites are removed and/or cleavage sites are mutated. See column 58, lines 15-27.

Barnett *et al.* do not disclose an intermolecular disulfide bond between cysteine residues introduced by mutations A492C and T596C, with reference to HIV subtype B, strain JR-FL. Neither do Barnett *et al.* specifically disclose affixing HIV-1 pre-fusion Env trimeric complex to the particle via an agent.

Binley *et al.* describe an isolated HIV-1_{JR-FL} envelope glycoprotein complex comprising a gp120 and gp41 bound to one another by a disulfide bond between a cysteine residue introduced by an A492C mutation into gp120 and a cysteine residue introduced by a T596C mutation into gp41 (¶127, ¶129, and ¶130), wherein the gp41 further comprises a mutation at the N-terminal helix, P600C (¶275). The modified gp120 further comprises a mutated furin cleavage site (¶67) and is characterized by the presence of one or more canonical glycoylation sites not present in wild type gp120, or by the absenceof one or more canonical glycosylation sites present in wild type gp120 (¶114-115). Binley *et al.* further describe a trimer comprising three identical modified

proteins of gp120 bound to gp41, a composition comprising an adjuvant and the HIV envelope complex or the trimer (Claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV Env composition of Barnett *et al.* by introducing stabilizing disulfide bond between A492C mutation into gp120 and T596C mutation into gp41, as taught by Binley *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of the HIV Env composition. There would have been a reasonable expectation of success, given that the stabilized trimeric gp120-gp41 complex is a better antigenic mimic of the native form and hence elicits a more relevant immune response to HIV, as taught by Binley *et al.*

Ishikawa *et al.* suggest formation of immune complexes on solid phase. See abstract. Specifically, Ishikawa *et al.* describe that antibody IgGs to HIV-1 were reacted with polystyrene beads coated successively with affinity-purified (anti-2,4-dinitrophenyl group) IgG and 2,4-dinitrophenyl-HIV-1 antigen conjugates and subsequently with HIV-1 antigen-β-D-galactosidase conjugates. See Materials and Methods, p. 228-229.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Barnett by affixing the HIV-1 gp120-gp41 trimer to a particle via an IgG as taught by Ishikawa *et al.* The skilled artisan would have been motivated to do so to further stabilize the trimeric conformation of HIV-1 gp120-gp41 complex. There would have been a reasonable expectation of success, given the rapid formation of the immune complexes on the polystyrene beads, as taught

by Ishikawa *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Since the prior art material meets the claim limitation of PLG, the prior art PLG would necessarily have the mean diameter from about 10 nm to 100 pm. Where, as here, the Patent Office lacks the facilities to perform comparisons between the claimed material and prior art materials that reasonably appear to meet the claim limitations, the burden is properly shifted to applicant to distinguish the claimed product from the prior art product. See *In re Best, Bolton, and Shaw*, 195 USPQ 430 (CCPA 1977); *Ex Parte Gray*, 10 USPQ2nd 1922 (BPAI 1989).

Applicant argues that one skilled in the art would not utilize the teachings of Ishikawa, *i.e.* an improved immunoassay, to make applicants' claimed composition, which is formulated for its intended purpose, *e.g.* administration to a subject to inhibit HIV infection of cells, not for detection of a captured antigen on a solid support. However, the improved signal from an immunoassay is an indication of enhanced immunogenicity of the antigen. The teachings in the Ishikawa reference show increased immunogenicity when HIV-1 antigen is affixed to a particle like a polystyrene bead via an agent such as IgG, which is the motivation for a skilled artisan to modify the trimeric HIV-1 gp140 complex taught by the Barnett and Binley group.

In other words, Applicant argues that the combination of references is not proper as there is no suggestion of the desirability of the combination in the art relied upon. This is not the standard for establishing a prima facie case of obviousness. The suggestion to combine or modify the teaching of the prior art can be established either

in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

To establish a *prima facie* case of obviousness, the Board must, *inter alia*, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." *Kotzab*, 217 F.3d at 1370, 55 USPQ2d at 1317.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
15 January 2008

Louise Humphrey, Ph.D.
Assistant Examiner